REMARKS

Claims 8-34, 50-51, 53-92, 118-119, and 159-162 are pending in the present application. By virtue of this response, claim 161 has been amended, and new claims 178-194 have been added. Claim 161 is amended to be in independent form. Support for new claims 178, 185-188, and 190-193 is found, *inter alia*, in original filed claims 52, 35, 38-40, 41, and 44-46. Support for new claims 179, 182, 184, 189, and 194 is found, *inter alia*, in the specification on page 56, lines 25-27, and page 81, lines 23-24. Accordingly, claims 8-34, 50-51, 53-92, 118-119, 159-162, and 178-192 are currently under consideration.

With respect to all claim amendments and cancellations, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Newly added claims

Applicants respectfully note that newly added claims 185-188, 190-193, and 178 correspond to original filed claims 35, 38-40, 41, 44-46, and 52, which are claims in Group IV and Group V of the Restriction Requirement issued to U.S. application 09/526,333 (now issued U.S. Pat. No. 6,566,118) from which this application claims priority. In a telephone call on May 29, 2003, the Examiner indicated that these claims could be presented for consideration of rejoinder. Since Applicants believe that no additional search is necessary for these new claims, Applicants respectfully request that these claims be rejoined in this application. The Examiner is invited to compare pending claim 50 to new claim 185, and pending claim 159 to new claim 190.

Telephone interview

Applicants thank Examiner Hill and Examiner Housel for extending the courtesy for a telephone interview on April 17, 2003, with Applicants' representatives and for providing helpful suggestions, which are reflected in this response. Examiner Housel indicated that Applicants are not required to provide a detailed interview summary.

Rejections and objections withdrawn

Applicants acknowledge with appreciation that the Examiner has withdrawn all previous objections and rejections under 35 U.S.C. §112, second paragraph, and previous rejections under 35 U.S.C. §103 not included in the current Office Action.

Rejections under 35 U.S.C. § 102

Claims 8, 9, and 17-20 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by O'Riordan (WO 97/08298). Specifically, the Examiner states that O'Riordan teaches uses of filtration to clarify lysates and ion-exchange and other types of columns to purify and concentrate rAAV particles. The Examiner alleges that O'Riordan discloses the sequential combination chromatography as cation then anion (i.e., DEAE ion-exchange chromatography followed by Cellufine® sulfate chromatography) in a preferred embodiment on page 21, lines 11-15.

Applicants respectfully traverse this rejection.

Applicants respectfully submit that O'Riordan et al. do not teach or suggest purification of rAAV particles using a combination of opposing ion exchange chromatography from AAV producer cell lysates or supernatants as claimed in the present invention. To anticipate a claim, the reference must teach every element of the claim. MPEP §2131. As the Examiner pointed out in the interview, O'Riordan et al. disclose the sequential combination chromatography for purification of AAV of DEAE ion-exchange and Cellufine® sulfate chromatography. O'Riordan et al., page 21, lines 11-15. DEAE ion-exchange is a positively-charged anion exchange column.

O'Riordan et al., page 37, line 16. As discussed during the telephone interview, O'Riordan et al. describe that "Cellufine® sulfate comprises a cellulose matrix with sulfonate groups esterified at the number-6 carbon of the repeating glucose subunits" and "binding of proteins to this resin is thought to occur through the polysaccharide moieties thereof". O'Riordan et al., page 30, lines 2-7. O'Riordan et al. also state that adenovirus should not bind to Cellufine® sulfate while most cellular glycoproteins would because adenovirus is a non-enveloped virus with no surface glycoproteins. O'Riordan et al., page 30, lines 7-10. Thus, Cellufine® sulfate is not characterized as an ion exchange resin by O'Riordan et al. Instead, O'Riordan et al. suggest that Cellufine® sulfate is an affinity resin based on interactions between glycoproteins and polysaccharide moieties of the resin. In addition, Cellufine® sulfate was not among the list of anion-exchange and cation-exchange resins listed by O'Riordan et al. Page 15, lines 11-33. In Example 11 of O'Riordan et al., DEAE chromatography was characterized as an anion exchange, but Cellufine® sulfate was not characterized as any type of ion exchange resin. There is no indication in O'Riordan et al. that Cellufine® sulfate was used as an ion exchange resin. Thus, O'Riordan et al. do not teach use of a combination of opposing ion exchange chromatography for purification of rAAV particles as claimed.

In view of the above, Applicants respectfully request the rejection of claims 8, 9, and 17-20 under 35 U.S.C. § 102(b) be withdrawn.

Rejections under 35 U.S.C. § 103

A. Claims 10-12 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over O'Riordan (WO 97/08298). The Examiner alleges that O'Riordan teaches the use of multiple columns including cation and anion chromatography as well as hydroxyapatite columns. The Examiner also alleges that it would have been obvious to one of ordinary skill in the art and a matter of routine laboratory optimization to change the order of columns in the protocol of O'Riordan to obtain AAV with a higher level purity.

Applicants respectfully traverse this rejection.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established. To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. These requirements are summarized in the MPEP (MPEP §2143, and §2143.01 to §2143.03), and are based on well-settled case law: *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Applicants respectfully submit that the cited reference does not teach or suggest all of the claimed limitations. As discussed above, Cellufine® sulfate is not characterized as an ion-exchange resin in O'Riordan et al. Ceramic hydroxyapaptite disclosed in O'Riordan et al. is not an ion-exchange resin, which is known by one skilled in the art. Since O'Riordan et al. do not teach or suggest purification of rAAV particles using a combination of opposing ion exchange chromatography from AAV producer cell lysates as discussed above, O'Riordan et al. do not teach or suggest all the claim limitations in claim 8 which claims 10-12 depend from. Thus, the obviousness rejection may be properly withdrawn on this ground.

In view of the above, Applicants respectfully request that the rejection of claims 10-12 under 35 U.S.C. §103(a) be withdrawn.

B. Claims 13-16 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over O'Riordan (WO 97/08298). The Examiner alleges that while O'Riordan does not teach tangential flow filtration specifically for AAV, it is taught as a method to concentrate

adenovirus. The Examiner also alleges that tangential flow filtration is known in the art as way to concentrate a sample and has been used for viruses. The Examiner argues that it would have been obvious to one of ordinary skill in the art to process the fluid samples of virus to facilitate the handling of larger volumes of fluid when doing column chromatography.

Applicants respectfully traverse this rejection.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established. To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. As discussed above, since O'Riordan et al. do not teach or suggest purification of rAAV particles using a combination of opposing ion exchange chromatography from AAV producer cell lysates as claimed in the present invention, O'Riordan et al. do not teach or suggest all the claim limitations in claim 8 which claims 13-16 depend from. Thus, the obviousness rejection may be properly withdrawn on this ground.

In view of the above, Applicants respectfully request that the rejection of claims 13-16 under 35 U.S.C. §103(a) be withdrawn.

C. Claim 21 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over O'Riordan (WO 97/08298) and Graham (*J. Gen. Virol* 1987, 68:937-940). The Examiner alleges that O'Riordan teaches the use of multiple columns including cation and anion chromatography and Graham teaches that cells grown in suspension offer advantages over cells grown in monolayers in terms of efficiency, economy and potential automation of large scale production. The Examiner argues that it would have been obvious to one of ordinary skill in the art to increase the amount of AAV to be purified by the method of O'Riordan by using the cell culture method of Graham.

Applicants respectfully traverse this rejection.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established. To establish a *prima facie* case of obviousness, the prior art reference (or references

when combined) must teach or suggest all the claim limitations. As discussed above, O'Riordan et al. do not teach or suggest purification of rAAV particles using a combination of opposing ion exchange chromatography from AAV producer cell lysates as claimed in the present invention. Graham does not cure the deficiencies of O'Riordan et al. Graham does not teach or suggest purification of AAV particles, let alone using a combination of opposing ion exchange chromatography for purification of rAAV particles. Graham discloses growth of host cells in suspension. Since O'Riordan et al. and Graham when combined do not teach or suggest all of the claim limitations of claim 8 and claim 21 which depends from claim 8, Applicants respectfully submit that a *prima facie* case for obviousness has not been established. Thus, the obviousness rejection may be properly withdrawn on this ground.

In view of the above, Applicants respectfully request that the rejection of claim 21 under 35 U.S.C. §103(a) be withdrawn.

D. Claims 50, 51, and 53-92 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over O'Riordan (WO 97/08298) and Graham (*J. Gen. Virol* 1987, 68:937-940), and further in view of Shenk (U.S. Patent No. 5,346,146). The Examiner contends that it would have been obvious to one of ordinary skill in the art to use a known method to construct rAAV such as the method of Shenk to make AAV to purify by the method of O'Riordan and scale up the cell culture with the advantages as taught by Graham.

Applicants respectfully traverse this rejection.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established. To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Claim 50 recites purification steps of chromatographing the AAV producer cell lysate on at least one positively-charged anion exchange resin followed by purifying the fractions containing rAAV particles by cation exchange chromatography or tangential flow filtration to generate a purified population of rAAV particles. As discussed above, O'Riordan et al. do not teach or suggest purification of rAAV

particles using at least one positively-charged anion exchange chromatography followed by cation exchange chromatography as claimed in claim 50. Although O'Riordan et al. teach use of tangential flow filtration to concentrate adenovirus, O'Riordan et al. do not teach that tangential flow filtration is useful for purifying AAV (e.g., separating AAV from adenovirus).

Applicants respectfully submit that "purifying" is distinct from "concentrating". "Purifying" an AAV particle in this context (and as the specification discloses) means isolating or separating the AAV particle from cellular proteins and other contaminants, such as helper virus (adenovirus), and helper virus proteins. Page 51, lines 1-6. In contrast, concentrating using a tangential flow filtration as discussed in O'Riordan et al. means reducing volume, thereby increasing concentration of virus. In addition, O'Riordan et al. only teach use of tangential flow filtration prior to chromatographic fraction techniques. O'Riordan et al., Page 10, lines 4-9. O'Riordan et al. do not teach or suggest chromatographing the AAV producer cell lysate on at least one positively-charged anion exchange resin followed by tangential flow filtration for further purification.

Shenk et al. do not cure the deficiencies of O'Riordan et al. Shenk et al. do not teach or suggest use of chromatography for purification of AAV. Instead, Shenk et al. teach a method of producing stocks of rAAV.

Graham does not cure the deficiencies of O'Riordan et al. and Shenk et al. Graham does not teach or suggest use of chromatography for purification of AAV. Graham teaches 293 cells grown in suspension culture offers advantages over monolayer cultures in terms of efficiency and economy as well as a potential for automation. Since O'Riordan et al., Shenk et al., and Graham when combined do not teach or suggest all of the claim limitations of claim 50 and claims 51, 53-92 which depend from claim 50, the Examiner has not set forth a *prima facie* case for obviousness. Thus, the obviousness rejection may be properly withdrawn on this ground.

To establish a *prima facie* case of obviousness, there must be a reasonable expectation of success. O'Riordan et al. state that using DEAE anion exchange chromatography is not enough for generating purified AAV. O'Riordan et al., page 38, lines 7-11 (stating that "there were still

some contaminating proteins present" after DEAE anion exchange chromatography and the fraction is further purified using other chromatography). O'Riordan et al. only teach use of tangential flow filtration for concentrating adenovirus fractions and do not teach or suggest that tangential flow filtration can be used for further purifying AAV. Thus, one skilled in the art would not have a reasonable expectation that using an anion exchange chromatography followed by a tangential flow filtration is effective in purifying AAV from adenovirus as well as adenoviral and cellular proteins as taught by the present invention. Page 81, lines 16-28. The obviousness rejection may be properly withdrawn on this ground.

In view of the above, Applicants respectfully request that the rejection of claims 50, 51, and 53-93 under 35 U.S.C. §103(a) be withdrawn.

Nonstatutory Double Patenting Rejections

Claims 22-34, 118-119, and 159-162 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 126 and 159-162 of allowed U.S. Patent Application No. 09/526,333 (now issued U.S. Pat. No.6,566,118).

Applicants will address this issue after Office's determination of allowable claims.

Applicants also wish to bring to the Examiner's attention co-owned, co-pending U.S. Application No. 10/020,482.

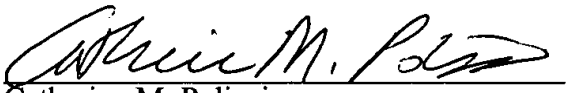
CONCLUSION

Applicant has, by way of the amendments and remarks presented herein, made a sincere effort to overcome rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 226272003310.

Respectfully submitted,

Dated: June 24, 2003

By: 

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